ELSEVIER

Journal of Cystic Fibrosis 12 (2013) 761 – 765

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

Prevalence of *Helicobacter pylori* infection in patients with cystic fibrosis

Sławomira Drzymała-Czyż [a], Jarosław Kwiecień [b], Andrzej Pogorzelski [c], Marta Rachel [d], Tomasz Banasiewicz [e], Andrzej Pławski [f], Aleksandra Szczawińska-Popłonyk [g], Karl-Heinz Herzig [h,i], Jarosław Walkowiak [a,*]

[a] *Department of Pediatric Gastroenterology and Metabolism, Poznań University of Medical Sciences, Szpitalna 27/33, 60-572 Poznań, Poland*
[b] *Department of Pediatrics, The School of Medicine and Division of Dentistry in Zabrze, Medical University of Silesia in Katowice, 3 Maja 13/15, 41-800 Zabrze, Poland*
[c] *Department of Bronchology & Cystic Fibrosis, National Institute for Tuberculosis & Lung Diseases, Prof. Jana Rudnika 3B, 34-700 Rabka, Poland*
[d] *Out-Patient Clinic of Alergology, Provincial Hospital No 2, Lwowska 60, 35-301 Rzeszów, Poland*
[e] *Chair of General Gastroenterological and Endocrinological Surgery, Poznań University of Medical Sciences, Przybyszewskiego 49, 60-355 Poznań, Poland*
[f] *Institute of Human Genetics, Polish Academy of Sciences, Strzeszyńska 32, 60-479 Poznań, Poland*
[g] *Department of Pediatric Pneumonology, Allergology and Clinical Immunology, Poznań University of Medical Sciences, Szpitalna 27/33, 60-572 Poznań, Poland*
[h] *Institute of Biomedicine & Biocenter of Oulu, University of Oulu, 90014 Oulu, Finland*
[i] *Department of Psychiatry, Kuopio University Hospital, 70211 Kuopio, Finland*

Received 15 June 2012; received in revised form 7 January 2013; accepted 8 January 2013
Available online 1 February 2013

Abstract

Introduction: Helicobacter pylori (*H. pylori*) is one of the most common bacterial infections worldwide. The prevalence of *Hp* infection in cystic fibrosis (CF) is unclear. Thus, the aim of our study was to determine the prevalence of *H. pylori* infection in CF patients and to correlate *H. pylori* presence with CF expression.
Material and methods: The presence of *H. pylori* infection was assessed using a breath test with isotope-labeled urea in CF 79 patients compared to 302 healthy control subjects (HS).
Results: Fifteen (19.0%) CF patients were *H. pylori* positive. No statistical differences in the basic clinical parameters or in their distribution were documented. No clinical factor was an independent risk factor of *H. pylori* infection. The corrected prevalence of *H. pylori* infection in pediatric CF patients and HS was 14.4% and 9.8%, respectively.
Conclusion: The prevalence of *H. pylori* infection in CF patients is not different from that in healthy subjects.

Keywords: Prevalence; *Helicobacter pylori*; Cystic fibrosis; Epidemiology

1. Introduction

Helicobacter pylori (*H. pylori*) is one of the most common chronic bacterial infections world-wide [1]. However, the prevalence of *H. pylori* infection is not homogeneous. In Western countries, the prevalence of *H. pylori* infection has been decreasing during the past few decades [2,3]. Nowadays, the prevalence of *H. pylori* infection in European studies varies between 7% in asymptomatic children in the Czech Republic and 33% in Northern Norway [4,5]. In Poland, during 2005–2006, *H. pylori* infection was diagnosed in 15.7% of children [6]. There was no difference in the mean age of the infected and the non-infected children.

H. pylori infection is acquired early in life and in the absence of antibiotic therapy, it generally persists for life. It is widely accepted that *H. pylori* infection is one of the main etiological factor for gastritis and peptic ulcer disease. Its eradication is

* Corresponding author. Tel.: +48 61 8480 310; fax: +48 61 8483 362.
E-mail address: jarwalk@ump.edu.pl (J. Walkowiak).

1569-1993/$ -see front matter
http://dx.doi.org/10.1016/j.jcf.2013.01.004

associated with ulcer healing and reduction of ulcer recurrence. Corpus gastritis is associated with a reduction in gastric acid, multifocal gastric atrophy and an increased risk of gastric cancer [7–10]. However, there are only few studies assessing prevalence of *H. pylori* infection in patients with cystic fibrosis (CF). Moreover, the results of these studies are sparse and contradictory [1,11–13].

Przyklenk et al. documented that prevalence of serum IgG antibodies against *H. pylori* was the same in CF patients and in the non-CF group [11]. The authors emphasized that frequency and length of prophylactic use of antibiotics did not decrease the prevalence of elevated serum antibodies against *H. pylori*, although the majority of antibiotics usually given to CF patients show a high in vitro activity against *H. pylori*. On the contrary, Littlewood et al. found an increased prevalence of *H. pylori* in the CF population [12]. Yahav et al. reported that the prevalence of *H. pylori* infection in CF patients (aged 1–44) was lower (16.6%) than in the age-matched non-CF controls (30.0%) assessing the *H. pylori* antigen by using specific monoclonal antibodies in stool specimens [13]. However, the observed difference was not statistically significant (p=0.118). Clearly, different tests have been previously used to determine the prevalence of *H. pylori* infections in CF patients. The serum test has been criticized not to predict an active infection.

2. Aim

The aim of the study was to determine the prevalence of *H. pylori* infection in CF patients.

3. Material and methods

The study population consisted of 79 CF patients (38 males & 41 females) 2 to 39 years of age, who did not receive intravenous or oral antibiotics (with the exception of azithromycin) or proton pomp inhibitors (PPI) for 3 months prior to the investigation.

The control group consisted of 302 healthy subjects, 3–18 years of age, who did not receive intravenous or oral antibiotics or PPIs for four weeks prior to the investigation. The investigation was part of the project PL0361 "Good diagnosis – treatment – life" by the First Specialist Clinical Hospital in Zabrze evaluating the incedences of gastrointestinal diseases in randomly selected children [14].

The genotypes of the studied CF patients were as follow: F508del/F508del (n=36), F508del/− (n=14), F508del/2143delT (n=3), F508del/CFTRdel2,3 (21 kb) (n=2), F508del/2183AA>G (n=3), F508del/3849+10kbc>T (n=2), F508del/1717-1G-A (n=2), F508del/N1303K (n=1), F508del/3272-26A>G (n=1), F508del/3659delC (n=1), F508del/G1244E (n=1), F508del/G542X (n=1), F508del/R553X (n=1), G542X/− (n=2), N1303K/− (n=1), N1303K/3272-26A>G (n=1), R533X/− (n=1), 3849+10kbc>T/− (n=1), non detected −/− (n=5) [15].

In all CF patient's *Z-score* for body height and weight, fecal elastase-1 concentration, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), International Normalized Ratio (INR) and frequency of *Pseudomonas aeruginosa* (*P. aeruginosa*) colonization were assessed. FEV1 was determined in subjects older than 6 years (Table 1). In patients with fecal elastase-1 concentrations higher than 100 μg/g, fecal fat excretion was determined to prove pancreatic sufficiency [16,17]. In addition, the socioeconomic status (urban or rural region) and genotype of CF patients were assessed.

The presence of *H. pylori* was assessed in all subjects using the ^{13}C isotope-labeled urea breath test (UBT). The test was performed after a minimum fast of 6 h. Two breath samples were collected as baseline and 30 min after swallowing (drinking) a 200 ml of orange juice drink which contained 50 mg of ^{13}C-labeled urea. To collect the breath samples, 650 ml aluminized bags connected to one-way valves were used. Measurement of the $^{13}CO_2/^{12}CO_2$ ratio was carried out using an ^{13}C-infrared isotope analyser system (IRIS, Wagner Analysen Technik, Bremen, Germany) with a cut-off value of delta over baseline (DOB)=4‰ [18].

The relationship between clinical status and *H. pylori* infection was assessed in all CF patients. The comparison of the prevalence of *H. pylori* infection in CF population (n=72) and healthy age matched subjects is depicted in Table 2.

4. Statistical methods

The comparison of the clinical parameters in patients with/without *H. pylori* infection was performed using the Mann–Whitney test. The difference in distribution of the *H. pylori* status between groups with different genotypes, with/without *P. aeruginosa* colonization, pancreatic sufficiency/insufficiency and socioeconomic status was analyzed by the χ^2 test. The influence of clinical parameters on the presence/absence of *H. pylori* infection was determined with the use of the logistic regression analysis. P value <0.05 was considered statistically

Table 1
Clinical and demographic data of CF patients.

Clinical parameters	All CF patients	Pediatric CF patients
Age [years] median (1–3 quartile)	13.6 (8.0–17.2)	10.3 (6.6–15.3)
Sex Males/females	38/41	29/33
Z-score for body height median (1–3 quartile)	−0.84 (−2.21–0.60)	−0.86 (−2.28–0.01)
Z-score for body weight median (1–3 quartile)	−0.86 (−1.47 to −0.43)	−0.89 (−1.48 to −0.34)
ALT [U/l] median (1–3 quartile)	25.0 (19.0–34.0)	25.5 (19.0–32.2)
AST [U/l] median (1–3 quartile)	31.0 (23.0–40.0)	31.0 (24.0–40.2)
INR median (1–3 quartile)	1.05 (1.02–1.12)	1.06 (1.02–1.12)
FEV1 [%] median (1–3 quartile)	71.5 (47.2–88.5)	72.0 (52.0–95.0)

Table 2
Number of children in the age group.

Aged (years)	CF patients (N)	Healthy subjects (N)
3–6	16	160
7–12	19	136
13–18	27	60

significant. All statistical analyses were performed using Statistica 9.0 software.

5. Ethical considerations

The protocol of the investigation was approved by the Institutional Review Board at Poznan University of Medical Sciences, Poland.

6. Results

H. pylori infection was diagnosed in 15 out of 79 (19.0%) CF patients aged 3 to 39 years (Table 3). In the 3 to 18 years age group a significantly higher percentage ($p<0.048$) of CF patients (16.1%) than healthy subjects (9.6%) were *H. pylori* positive. However, after the correction for the number of patients in the age subgroups the prevalence of *H. pylori* infection (14.4% vs 9.8%) did not differ ($p<0.173$).

No statistical differences in clinical parameters between *H. pylori* positive and negative subgroups were detected (Table 4). The distribution of genotype, *P. aeruginosa* colonization, socioeconomic status (urban v.s. rural region) and pancreatic sufficiency was comparable in the studied CF subgroups (Tables 5–7).

In the logistic regression analysis no clinical factor was found to be an independent risk factor of *H. pylori* infection.

7. Discussion

There are very few reports on the prevalence of *H. pylori* infection in CF patients in the literature [11–13]. Moreover, *H. pylori* infection was assessed by an unreliable method [11] or the group size of CF patients was very small [13]. Therefore, in the present study we assessed a large group of CF patients using UBT as a gold standard [19] and compared the results with age matched healthy control subjects.

Table 3
Prevalence of *H. pylori* infection in CF patients and in healthy subjects.

Age		*H. pylori* positive		Statistical significance
		CF patients n (%)	Healthy subjects n (%)	
3–6		0 (0%)	4 (3.7%)	0.810
7–12		4 (21.1%)	16 (11.0%)	0.258
13–18		6 (22.2%)	9 (15.0%)	0.409
All together	Raw data	10 (16.1%)	29 (9.6%)	0.048
	Corrected value *	14.4%	9.8%	0.173

* For the number of patients in age subgroups.

Table 4
H. pylori (*Hp*) infection and clinical parameters in CF patients.

Clinical parameters	*Hp* positive	*Hp* negative	Statistical significance
Age [years] median (1–3 quartile)	14.6 (12.0–19.9)	13.2 (6.8–16.9)	n.s.
Z-score for body height median (1–3 quartile)	−0.87 (−2.28 to −0.45)	−0.85 (−2.21–0.08)	n.s.
Z-score for body weight median (1–3 quartile)	−0.86 (−2.01 to −0.60)	−0.85 (−1.41 to −0.41)	n.s.
ALT [U/l] median (1–3 quartile)	25.0 (17.0–31.0)	25.5 (19.0–35.8)	n.s.
AST [U/l] median (1–3 quartile)	30.0 (18.0–41.0)	31.0 (23.3–39.8)	n.s.
INR median (1–3 quartile)	1.07 (1.03–1.19)	1.05 (1.01–1.12)	n.s.
FEV1 [%] median (1–3 quartile)	75.0 (49.0–89.0)	69.5 (51.0–88.5)	n.s.

Serum tests detecting antibodies against *H. pylori* are not differentiating between active or previous exposure [20]. *H. pylori* antibodies were detected in 30.4% of 3435 healthy Polish children (age 0 to 18 years) [21,22]. Płonka et al. also found a higher percentage of *H. pylori* infection in asymptomatic children as we did in the present study [23]. 26.0% of healthy children (age 6 to17), living in urban and 21.6% in rural areas (Polish Tatra Mountains) had active *H. pylori* infections as documented by positive UBTs. Krusiec-Świdergoł et al., found a similar prevalence of 15.7% *H. pylori* infection in healthy, asymptomatic school children (age 7 to 15 years) using the same method [6]. In the present study, the prevalence of infection in CF patients was comparable to that of healthy subjects and independent of their socioeconomic status. Thus, it seems that prevalence of *H. pylori* infection in CF patients and healthy subjects is very similar.

Przyklenk et al. studied 263 CF patients (age 6 months to 34 years) and 168 age matched healthy controls and found a prevalence of serum IgG *H. pylori* antibodies in 19.0% and 18.0%, respectively [11]. Yahav et al. reported a prevalence of *H. pylori* infection in CF patients and a non-CF control group

Table 5
H. pylori infection and distribution of *P. aeruginosa* (*Pa*) colonization, pancreatic sufficiency and socioeconomic status.

Clinical parameters		*H. pylori*		Statistical significance
		Positive n (%)	Negative n (%)	
Pa colonization	Yes	9 (21.5%)	33 (78.5%)	n.s.
	No	6 (16.2%)	31 (83.8%)	
Pancreatic sufficiency	Yes	3 (33.3%)	6 (66.7%)	n.s.
	No	12 (17.2%)	58 (82.8%)	
Socioeconomic status	Urban	5 (11.9%)	37 (88.1%)	n.s.
	Rural	10 (27.0%)	27 (73.0%)	

Table 6
The prevalence of *H. pylori* infection in CF patients with different genotypes.

CF mutations	*H. pylori*		Statistical significance
	Positive n (%)	Negative n (%)	
Severe/severe	10 (19.6%)	41 (80.4%)	n.s.
Others	5 (17.8%)	23 (82.2%)	

of 16.6 and 30.0%, respectively using *H. pylori* antigen detection in stool [13]. Yet, because of the small number of CF patients (n=30), the observed difference did not reach statistical significance. In the present study, the prevalence of *H. pylori* infection in CF patients (age 3–18 years) was significantly higher ($p<0.048$) than in the control group (16.1% and 9.6%, respectively). However, there were more CF patients in the older age subgroups. With the correction for age, the prevalence of *H. pylori* infection was 14.4% and 9.8%, respectively and thus not any longer statistically significant ($p<0.173$).

We did not find any significant relationship between the CF genotype and *H. pylori* colonization. However, the management of mild and severe CF patients differs and may potentially have an impact on clearing previous infection. Yahav et al. noted that prevalence of *H. pylori* in pancreatic sufficient CF patients was higher in comparison to patients with pancreatic insufficiency (75.0% and 7.6%, respectively) [13]. However, only 4 out of their 30 CF patients were pancreatic sufficient. The authors suggested that *H. pylori* infection in CF patients with pancreatic insufficiency is less frequent because these patients have a more severe disease form requiring intensive antibiotic therapy. In addition, *H. pylori* colonization may have been reduced due to prolonged secretion of abnormal gastric mucus which is denser and contains more fructose, galactose, and N-acetylglucosamine [13,24,25]. Furthermore, we did not find any statistical difference between pancreatic sufficient and insufficient patients in the present study. Furthermore, we did not observe a relationship between the prevalence of *P. aeruginosa* colonization and *H. pylori* infection. Our results are in agreement with those published by Przyklenk et al. who found a similar prevalence of chronic *P. aeruginosa* colonization in *H. pylori* positive and negative subgroups [11].

In conclusion, the prevalence of *H. pylori* infection in CF patients was not different from that in healthy subjects. There was no significant relationship between the clinical expression of disease in CF and *H. pylori* colonization.

Table 7
The prevalence of *H. pylori* infection in CF patients with F508del and other mutations.

CF mutations	*H. pylori*		Statistical significance
	Positive n (%)	Negative n (%)	
F508del/F508del	7 (19.4%)	29 (80.6%)	n.s.
F508del/other	6 (18.7%)	26 (81.3%)	
Other genotype	2 (18.2%)	9 (81.8%)	

Acknowledgments

The authors declare that they have no conflict of interest.

The study was supported by the grants from the Poznań University of Medical Sciences (No. 502-01-1103603-07588).

References

[1] Cohen TS, Prince A. Cystic fibrosis: a mucosal immunodeficiency syndrome. Nat Med 2012;18:509–19.
[2] Mourad-Baars P, Hussey S, Jones NL. Helicobacter pylori infection and childhood. Helicobacter 2010;15:53–9.
[3] Ford AC, Axon AT. Epidemiology of *Helicobacter pylori* infection and public health implications. Helicobacter 2010;15:1–6.
[4] Sykora J, Siala K, Varvarovska J, Pazdiora P, Pomahacova R, Huml M. Epidemiology of *Helicobacter pylori* infection in asymptomatic children: a prospective population-based study from the Czech Republic. Application of a monoclonal-based antigen-in stool enzyme immunoassay. Helicobacter 2009;14:286–97.
[5] Breckan RK, Paulssen EJ, Asfeldt AM, Mortensen L, Straume B, Florholmen J. The impact of body mass index and *Helicobacter pylori* infection on gastro-oesophageal reflux symptoms: a population-based study in Northern Norway. Scand J Gastroenterol 2009;44:1060–6.
[6] Krusiec-Świdergoł B, Kwiecień J, Jonderko K, Strój L, Kasicka-Jonderko A, Błońska-Fajfrowska B. Decreasing prevalence of *Helicobacter pylori* infection in children in Poland. Prz Gastroenterol 2010;5:279–84.
[7] Pacifico L, Anania C, Osborn JF, Ferraro F, Chiesa C. Consequences of *Helicobacter pylori* infection in children. World J Gastroenterol 2010;16:5181–94.
[8] Konturek PC, Konturek SJ, Brzozowski T. *Helicobacter pylori* infection in gastric cancerogenesis. J Physiol Pharmacol 2009;60:3–21.
[9] Shanks AM, El-Omar EM. *Helicobacter pylori* infection, host genetics and gastric cancer. J Dig Dis 2009;10:157–64.
[10] Jackson L, Britton J, Lewis SA, et al. A population-based epidemiologic study of *Helicobacter pylori* infection and its association with systemic inflammation. Helicobacter 2009;14:460–5.
[11] Przyklenk K, Bauernfeid A, Borscelm W, Bertele RM, Harms K, Arleth S. Seroimmunological monitoring of *Campylobacter pylori* in patients with cystic fibrosis. Serodiagn Immunother Infect Dis 1989;3:307–16.
[12] Littlewood JM. Cystic fibrosis: gastrointestinal complications. Br Med Bull 1992;48:847–59.
[13] Yahav J, Samra Z, Blau H, Dinari G, Chodick G, Shmuely H. *Helicobacter pylori* and *Clostridium difficile* in cystic fibrosis patients. Dig Dis Sci 2006;51:2274–9.
[14] Żabka A, Kwiecień J, Bąk-Drabik K, Krzywicka A, Porębska J, Pieniążek W. Does frequency of *H. pylori* in children 3–18 years old decrease? (Preliminary report). Probl Med Rodz 2010;2(32):18–20.
[15] Walkowiak J, Herzig KH, Witt M, et al. Analysis of exocrine pancreatic function in cystic fibrosis: one mild CFTR mutation does not exclude pancreatic insufficiency. Eur J Clin Invest 2001;31:796–801.
[16] Walkowiak J, Lisowska A. Pancreatic enzyme therapy and gastrointestinal symptoms in patients with cystic fibrosis. J Pediatr 2005;147:870–1.
[17] Walkowiak J, Nousia-Arvanitakis S, Agguridaki C, et al. Longitudinal follow-up of exocrine pancreatic function in pancreatic sufficient cystic fibrosis patients using the fecal elastase-1 test. J Pediatr Gastroenterol Nutr 2003;36:474–8.
[18] Machado RS, Patrício FR, Kawakami E. ^{13}C urea breath test to diagnose *Helicobacter pylori* infection in children aged up to 6 years. Helicobacter 2004;9:39–45.
[19] Koletzko S, Jones NL, Goodman KJ, et al. Evidence-based guidelines from ESPGHAN and NASPGHAN for *Helicobacter pylori* infection in children. J Pediatr Gastroenterol Nutr 2011;53:230–43.
[20] Weijnen CF, Hendriks HA, Hoes AW, Verweij WM, Verheij TJ, de Wit NJ. New immunoassay for the detection of *Helicobacter pylori* infection compared with urease test, ^{13}C breath test and histology: validation in the primary care setting. J Microbiol Methods 2001;46:235–40.

[21] Iwańczak F, Maciorkowska E, Kaczmarski M, et al. Epidemiological studies of frequency of *Helicobacter pylori infection* in children in Poland. Ped Wsp 2004;6:345–50.

[22] Iwańczak F, Iwańczak B, Pytrus T, Dworak O, Gościniak G, Vogtt E. Prevalence of *H. pylori* infection in the Polish child population. Pol Merkur Lekarski 2005;18:407–11.

[23] Płonka M, Bielański W, Konturek SJ, et al. *Helicobacter pylori* infection and serum gastrin, ghrelin and leptin in children of Polish shepherds. Dig Liver Dis 2006;38:91–7.

[24] Glass GB, Slomiany BL. Derangements of biosynthesis, production and secretion of mucus in gastrointestinal injury and disease. Adv Exp Med Biol 1977;89:311–47.

[25] Slomiany A, Liau YH, Carter SR, Newman LJ, Slomiany BL. Mucus glycoprotein fatty acyltransferase in patients with cystic fibrosis: effect on the glycoprotein viscosity. Biochem Biophys Res Commun 1985;132:299–306.